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Intractable convulsion in critically ill children

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ABSTRACT

Introduction: To determine the etiology of intractable convulsion, the outcome of intractable convulsions in pediatric patients and risk factors related to poor outcome.

Material and methods: This case-control study conducted on 100 children where 50 patients who fulfilled the criteria for intractability admitted into pediatric intensive care unit (PICU) and 50 epileptic children on appropriately chosen antiepileptic drug (AED) with no seizures for more than 1 year who attending to the pediatric neurology clinic for follow up. Full history taking, examination, investigations performed for patients groups on admission and then followed up to six months for an outcome.

Results: This study showed no significant difference between studied groups as regard age, sex, consanguinity and positive family history but noticed a highly statistically significant increase in prenatal problems (n; 20 patients), neonatal seizure (n; 15 patients), and postnatal problem (n; 10 patients) in intractable groups compared to controlled groups (p value 0.001). Delayed developmental history (n; 40 patients) was significantly higher among intractable groups compared to controlled groups (p value 0.001). Intractable groups had significantly increased in abnormal neurological examination than controlled groups (p value 0.001). History of prenatal problems, neonatal seizures, delayed developmental milestones, presence of underlying etiology of seizures, and abnormality findings in EEG and neuroimaging are risk factors for the intractability of convulsion. There was a significant relation between poor outcome and other studied variables including being female, presence of consanguinity, delayed developmental milestones, disturbed level of consciousness and secondary etiology of seizures (p value; 0.04, 0.003, 0.001, 0.001 0.001 respectively).

Conclusion: The most common etiology of intractability in epileptic children is a secondary etiology of seizures. Early detection of risk factors for intractable epilepsy is important to decrease intractability complications. Proper perinatal care is important for decreasing prevalence of intractable epilepsy.

Key words: convulsion; epilepsy; intractable convulsion; outcome

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Introduction

Convulsion is the most common neurological diseases in pediatric patients and account one time in 4–10% of children in the first 16 years of life [1]. Convulsion defined as a paroxysmal and transient occurrence of signs or symptoms resulting from abnormal neuronal activity originated in the brain [2].

Epilepsy is chronic brain diseases diagnosed by recurrent spontaneous convulsions, which start in the childhood period. Refractory and repeated convulsions can cause long-term cognitive impairment, lower of social participation and decreased quality of life. About 30% of patients with epilepsy; the convulsions are intractable, 70% of these patients become controlled with antiepileptic drugs [3].

Intractable convulsion is a life-threatening medical emergency that needs urgent recognition and emergency treatment to decrease morbidity and mortality. The predictors of the intractability of convulsions are the presence of a structural lesion, abnormal neurological state and early onset of convulsion [4].

The intractable convulsion diagnosed as a failure of adequate two or more tolerated, suitable chosen anticonvulsant drug schedules whether as monotherapies or in combination to achieve optimum freedom from convulsion [5].

The patients considered as intractable when they developed at least one convulsion or more per month in a 6-month period although being treated with at least 2 appropriately chosen antiepileptic drugs [6].

The aim of this study was to detect the etiology, risk factors related to intractability and poor outcome of convulsion in children.

Material and methods

The study was performed from September 2016 to July 2018 and was approved by the local Ethical Committee. A written informed consent for each child was obtained from their parents prior to inclusion. In this case-control study, 100 children enrolled in the study aged 12 months to 12 years old, where epileptic children were selected from PICU and outpatient clinic from the Pediatric Neurology Unit, Pediatric Department, Menoufia University Hospitals. These children were divided into two main groups, which included: Group I included 50 epileptic children who fulfilling the criteria for intractability, they were 18 males (36%) and 32 females (64%). Group II included 50 epileptic children on AEDs with no seizures for more than 1 year, they were 22 males (44%) and 28 females (56%). They underwent full history taking, clinical examinations and investigation.

Inclusion criteria in the study if patient involves any of the following; 1) Epileptic children with intractability (failure of 2 or more first-line antiepileptic drugs to control seizures in children who had 1 or more seizures per month for 2 years). 2) Age from 2 to below 18 years.

Exclusion criteria including one of these; Patients with single unprovoked seizures, Patients with provoked seizures, Patients with poor compliance regarding regular drug intake or appearance of drug side effects, Patients with unsuitable drug choice, and Patients with an inborn error of metabolism.

All patients subjected to full history taking including; age, sex, residence, consanguinity, family history of epilepsy, prenatal insult, neonatal seizure and developmental history. Clinical examination including; general examination (HR, RR, Temp, and B.P), anthropometric measurements in form of Wt. in kg, Ht. in cm, head circumference in cm, and body mass index and assessment of developmental milestones and examine neurological reflexes.

For all patients; laboratory investigations withdrawn including complete blood count (CBC), serum electrolytes (Na, K, and Ca), Neuroimaging study including CT, MRI and EEG. Eventually, All patients were followed up for 6 months after discharge from the Pediatric Intensive Care Unit (PICU).

Assessment of developmental milestones

Developmental milestones assessed according to the age of achievement of these milestones. To assess the onset of key developmental milestones without

having to complete an entire standardized assessment, urgent milestones from motor and language domains chosen. All questions took the format: 'At what age did he/she first...' and in this study, we use data from one 'early' and one 'late' milestone, e.g., 'Sit without support' and 'Walk independently' (gross motor), 'Pick up a small object with a pincer grip, i.e., with thumb and forefinger' and 'Stack at least three small blocks or other small objects; stack must not fall' (fine motor), 'Say their first word' and 'Put two or more words together' (language) [7].

Delayed milestone, also called **developmental delays**, considered when a child does not reach one of these stages at the expected age. But, in most cases, a wide variety of ages can be considered normal, and not a cause for medical concern. Milestones are often measured using percentiles, and for many milestones, a value between the 5th and 95th percentile does not require intervention, though values towards the edges of that range can be associated with other medical conditions. It is not possible to treat. The measurement of posture sway may be an early indicator [8].

Statistical analysis

Data were collected, tabulated, statistically analyzed using a personal computer with Statistical Package of Social Science (SPSS) (version 20; Inc., Chicago .IL) where the following statistics were applied. Two types of statistics were done: Descriptive statistics e.g. Number (No), percentage (%), mean (\bar{X}) and standard deviation (SD). The second was Analytic statistics: Chi-squared test (χ^2), student t-test (t), Kruskal Wallis test (K), one-way Anova test (F), Mann-Whitney test (U), P-value ≤ 0.05 to be statistically significant, P-value ≤ 0.001 to be highly statistically significant. Values were expressed as means and standard deviations or counts and percentages as appropriate.

Results

The socio-demographic data of studied groups showed no statistically significant difference between studied groups as regard age, sex, consanguinity and positive family history but showed a highly statistically significant increase in prenatal insult and postnatal problem in intractable groups compared to controlled groups ($p = 0.001$). Delayed developmental history was significantly higher among intractable groups compared to controlled groups ($p = 0.001$). Neonatal seizure in the form of partial seizures, myoclonic seizures and infantile spasms were more frequent in children with intractable convulsion (Tab. 1).

Neurological examination of studied groups showed a highly significant increase in neurological abnormality

Table 1. Socio-demographic data of all studied patients

Demographic data	Group I		Group II		X ²	p value
Age in years						
Range	1–12		3–12		0.74	0.45
Mean ± SD	4.1 ± 4.2		4.5±3.8			
Sex	No	%	No	%	2.3	0.59
Male	18	36	22	44		
Female	32	64	28	56		
Consanguinity	No	%	No	%	2.4	0.48
Positive	21	42	15	30		
Negative	29	58	35	70		
Family history of epilepsy	No	%	No	%	6.9	0.067
Positive	26	52	20	40		
Negative	24	48	30	60		
Prenatal problems	No	%	No	%	36.1	0.001*
NO insult	30	60	37	74		
Kernicterus	5	10	3	6		
Cyanosis	5	10	5	10		
Obstructed labor with HIE	10	20	5	10		
Neonatal seizure	No	%	No	%	28.7	0.001*
Positive	15	30	9	18		
Negative	35	70	41	82		
Postnatal problem	No	%	No	%	28.8	0.001*
Positive	10	20	8	16		
Negative	40	80	42	84		
Developmental history	No	%	No	%	74.2	0.001*
Normal	10	20	25	50		
Delayed	30	60	25	50		
Lost after being acquired	10	20	0	0		

X² — Chi square test; *statistically significant $p \leq 0.05$; HIE — Hypoxic Ischemic Encephalopathy; Group I — intractable epileptic patients; Group II — controlled epileptic patients

in intractable groups than controlled groups regarding mentality, speech, cranial nerve and motor system assessment ($p = 0.001$) (Tab. 2).

Also, this study noticed a highly significant difference between the two studied groups; intractable epileptic group and controlled epileptic group, regarding the number of antiepileptic drugs taken to control convulsions ($p = 0.001$) (Tab. 3).

History of prenatal problems, neonatal seizures, delayed developmental milestones, presence of underlying etiology of seizures, abnormality in Electro Encephalograms (EEG) and Neuroimaging studies are risk factors for the intractability of convulsion ($p = 0.001$) (Tab. 4).

As regarding the etiology of seizures, there was a significant increase in secondary causes in intractable groups than controlled groups ($p = 0.001$) (Tab. 5).

There was a significant relation between poor outcome and other studied variables including being

female, presence of consanguinity, delayed developmental milestones and disturbed level of consciousness and secondary etiology of seizures (Tab. 6).

Discussion

Intractable convulsions in children are a life-threatening disease with serious risk of neurological insults which considered a medical emergency [9]. Epilepsy accounts for more than 50% of children, and refractory epilepsy is a big problem in this age group [10].

Only 3% of children fail to respond to the first two anticonvulsants drugs become seizure-free by using a third anticonvulsant drug, while the convulsions become intractable in about one-third of these children [11].

In our study, there was highly statistically significant difference between the two groups as regarding

Table 2. Neurological examination of studied patients

Neurological examination	Group I		Group II		X2	p value
Mentality	N	%	N	%		
• Normal	18	36	35	70	38.2	0.001*
• Low	32	64	15	30		
Speech	N	%	N	%	36.2	0.001*
• Normal	15	30	35	70	40.7	0.001*
• Delayed	33	66	15	30		
• Couldn't be assessed	2	4	0	0		
Cranial nerve	N	%	N	%		
• Normal	33	66	40	80	84.0	0.001*
• Affected	17	34	10	20		
Motor system	N	%	N	%		
A. Power					34.0	0.001*
• Normal	25	50	25	50		
• Weakness	25	50	25	50		
B. Tone						
• Normal tone	25	50	38	76	34.0	0.001*
• Hypotonia	13	26	5	10		
• Hypertonia	12	24	7	14		

X² — Chi square test; *Statistically significant $p \leq 0.05$ **Table 3.** Response of studied groups to anti-epileptic drugs

Drug therapy	Group I		Group II		Test	p value
	N	%	N	%		
Monotherapy control	0	0	30	60	86.2	0.001*
Ditherapy control	0	0	20	40	66.8	0.005*
Polytherapy control	43	86	0	0	74.9	0.002*
Uncontrolled drug therapy	7	14	0	0	89.4	0.001*

X² — Chi-square test; *Statistically significant $p \leq 0.05$

mentality, speech and motor system affection and also; Tripathi et al. [12] and Saygiet al. [13] found that there was an underlying etiology that affects the brain and motor system.

Our results revealed that there was a significant statistical difference between studied groups regarding response to drugs (monotherapy, polytherapy), where all patients with intractable convulsions needed polytherapy. This agreed with Smith et al. [14] as the definition of intractability depend on failure of treatment with two (or more) tolerated, appropriately chosen and used antiepileptic drug schedules (whether as one drug therapy or in combination) to achieve sustained seizure free [5]. Presence of underlying neurologic deficit points to either the intrinsic severity of epilepsy or to the severity of underlying etiology. These two factors may account for pharmacy resistance noticed by Patil et al. [15].

We found that there was a significant difference between studied groups regarding etiology where the secondary type of epilepsy (66%) was more with intractable epileptic patients due to cerebral palsy (45.5%) and post-traumatic intracranial hemorrhage (18.2%). Kwan, et al. [16], Berg et al. [17] and Ohtsuka et al. [18] found that symptomatic epilepsy associated with intractability. In the study of Manoj et al. [19]; 71 % of intractable epileptic children had remote symptomatic etiology, perinatal asphyxia constituted almost 50% children of intractable seizures and was an important predictor for intractability. In the study of Moinuddin et al. [20]; hypoxic-ischemic damage of the brain due to perinatal asphyxia and cerebral palsy were the main causes of symptomatic epilepsy.

We found that the presence of the history of pre-natal problem, delayed developmental milestones, the secondary type of epilepsy, and neuroimaging studies abnormalities were risk factors for epilepsy intractability.

Table 4. Risk factors of intractable convulsion in all studied groups

Risk factors	Group I N = 50		Group II N = 50		X2	p value
	N	%	N	%		
Sex					0.66	0.041
Male	18	36	22	44		
Female	32	64	28	56		
History of prenatal problems					0.8	0.001*
	20	40	13	26		
Presence of consanguinity	21	42	15	30	1.5	0.21
Family history of convulsion or neurological disorder	26	52	20	40	1.2	0.02*
Abnormal developmental milestones	40	80	25	50	9.8	0.001*
History of neonatal seizures	15	30	9	18	9.1	0.002*
Presence of postnatal problem	10	20	8	16	0.27	0.60
Partial type of seizure or partial with secondary generalization	13	26	4	8	5.7	0.01*
Underlying etiology of seizures	33	66	25	50	2.6	0.001*
Abnormal EEG finding	39	78%	29	58%	4.5	0.03*
Abnormal neuroimaging studies	22	44%	10	20%	6.9	0.001*

*Statistically significant $p \leq 0.05$ **Table 5.** The most probable etiology of seizures among all studied patients

Etiology of epilepsy	Group I		Group II		X2	p value
	N	%	N	%		
Idiopathic	17	34	25	50	66.1	0.001*
Secondary	33	66	25	50	66.1	0.001*
Cerebral palsy	15	45.5	20	80	12.56	0.002*
Neurodegenerative	4	12.1	0	0		-
Congenital Malformation	5	15.1	0	0	3.184	FEp = 0.235
*Post neuro-infection sequelae	2	6.1	3	12	0.85	0.12
Post traumatic intracranial hemorrhage	6	18.2	2	8	0.64	0.012*
Abscess	1	3	0	0	-	-

X2 — Chi-square test; FE × Fisher Exact test; *statistically significant ≤ 0.05 ; *Post-neuro-infection — post meningitic, post-encephalitic

History of neonatal seizures associated with intractability risk caused by neuronal damage; during this period rapid brain development occur; so, most of these children demonstrate a history of prenatal asphyxia, congenital malformations and other factors that play an important role in the development of intractable epilepsy. accordingly type of neonatal seizures; partial seizures, myoclonic seizures and infantile spasms were more frequent in children with intractable convulsion and this agrees with the result of Joseph et al. [21]. Eriksson and Koivikko [22] stated that the presence of mixed seizure types, myoclonic seizures and infantile spasms may cause poor seizure control. In the study of Chawla et al. [23], there was an association between myoclonic seizures and intractability.

There were significant relations between delayed developmental milestones, decreased conscious level, and etiology of convulsions, electrolyte disturbance and poor outcome of patients. Camfield et al. [24] and Berg et al. [25] found that the underlying diagnosis was the major predictor of mortality and outcome. And also Shinnar [26] found that an underlying congenital cause or early childhood brain damage causing neurodeficits is a strong predictor for a poor long-term seizure outcome.

Conclusions

Intractable Convulsion results from primary central nervous system insult or systemic disease with sec-

Table 6. Relation between outcome with Socio-demographic data, clinical and etiology of intractable epileptic group

Socio-demographic data	Outcome for patient with intractable convulsion				X2	p value
	Poor		Good			
Sex	No	%	N	%	3.6	0.04
Male N = 18	8	16	10	20		
Female N = 32	23	46	9	18		
History of prenatal problems N = 13	9	18	4	8	0.3	0.8
Presence of consanguinity N = 21	8	16	13	26	8.7	0.003*
Family history of convulsion or neurological disorder N = 26	17	34	9	18	0.2	0.6
Abnormal developmental milestones N = 40	31	62	8	16	19.3	0.001*
Seizure type						
• Generalized N = 37	21	42	16	32	1.6	0.19
• Partial N = 13	10	20	3	6		
Conscious level						
• Conscious N = 24	5	10	19	38	29.3	0.001*
• Disturbed N = 26	26	52	-			
Associated electrolyte disturbance					12.1	0.002*
• Na N = 12	2	4	10	20		
• K N = 12	1	2	11	22		
• Ca N = 19	12	24	7	14		
Etiology					28.0	0.001*
Idiopathic N = 17	0	0	17	34		
Secondary N = 33	31	62	2	4		

X2 — Chi-square test; *Statistically significant $p \leq 0.05$

ondary central effect. The poor outcome associated with females more than males, in patients with a positive family history of epilepsy, delayed developmental milestones, patients with a disturbed conscious level and patients with secondary epilepsy.

Disclosure

The authors declare no financial or other conflicts of interest related to this work.

Ethical approval

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee.

Author's contributions

FM: participated in data acquisition, data interpretation and revision of the manuscript. **NS:** participated in study design, data analysis, data interpretation, drafting, revision of the manuscript and correspondence.

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